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Dated 26 August 2004

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20NOV03 E853697-1 B18476
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Request for grant of a patent

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2-20112003WW

2. Patent application number
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0327006.3

20 NOV 2003

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

WARREN WARD
MINDALE, FFORDD HENDRE
PRESTATYN LL19 8PG, UK

Patents ADP number *(if you know it)*

8677338001

If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention

DRUG COMPOSITION AND THERAPEUTICS

5. Name of your agent *(if you have one)* NO

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

~~WARREN WARD~~
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see FEIT 101104.

Patents ADP number *(if you know it)* 8458275001

6. Priority: Complete this section if you are declaring priority from one or more earlier patent applications, filed in the last 12 months.

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*
GB	0316940-6	19/JUL/03

7. Divisionals, etc: Complete this section only if this application is a divisional application or resulted from an entitlement dispute (see note f)

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8. Is a Patents Form 7/77 (Statement of inventorship and of right to grant of a patent) required in support of this request?

Answer YES if:

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Patents Form 1/77

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Continuation sheets of this form	0
Description	10
Claim(s)	3
Abstract	0
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Priority documents	0
Translations of priority documents	0
Statement of inventorship and right to grant of a patent (Patents Form 7/77)	0
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Request for a substantive examination (Patents Form 10/77)	0
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11. I/We request the grant of a patent on the basis of this application.

Signature(s) Warren Ward Date 19 NOV 2003

12. Name, daytime telephone number and e-mail address, if any, of person to contact in the United Kingdom

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DRUG COMPOSITION AND THERAPEUTICS

INTRODUCTION

The present invention relates to the treatment or prophylaxis of medical conditions by medications or nutritional supplements characterised by a formulation wherein the active ingredient or ingredients are made not to cross membrane barriers of mammals.

Many thousands of compounds are currently manufactured for use for therapeutic purposes. Naturally occurring substances, for example plant material, are also prepared for use for therapeutic purposes. For the present purpose, these compounds and substances are termed "drugs".

Drugs are almost always compounds foreign to the body. As such, they, unlike endogenous substances, are not continually being formed and eliminated. Drug absorption, bioavailability, distribution, and elimination are therefore determinants of onset, duration, and intensity of drug effect.

Drug absorption in mammals is determined by their physicochemical properties, their formulations and routes of administration. The actual dosage forms (e.g. tablets, capsules, solutions) consisting of the drug and suitable excipients are formulated to be administered by various routes including oral, buccal, sublingual, rectal, parenteral, dermal and inhalational. A prerequisite to absorption is drug dissolution. For example, solid drug products like tablets disintegrate and disaggregate quickly or slowly, but absorption can only occur after drugs enter solution.

Drugs are designed to enter systemic circulation to have the desired effect. Thus those skilled in the art of drug preparation are concerned to achieve effective transport across biological barriers, to control transit times, dissolution and absorption, and to maximise bioavailability in circulation and at the place of the therapeutic target. Some drugs cross the cell membrane to enter the cell itself.

Drugs in circulation may also metabolise in the body in a wide range of chemical reactions including oxidation, reduction, hydrolysis, hydration, conjugation, condensation and isomerisation and these reactions have to be carefully predicted. Unwanted metabolites may be difficult to eliminate from the body. There may also be harmful interactions with other drugs or with endogenous substances.

Drugs in circulation can accumulate over time in tissues or body compartments and thus cause undesirable effects. Drugs in circulation may penetrate areas where they would be harmful, such as across the blood-brain barrier or the placenta.

Therefore great skill is needed in the manufacture and testing of drugs, and the costs of formulating current drugs are very high, often hundreds of millions of pounds. Nevertheless, nearly all drugs in body circulation can have undesirable side effects, and may harm the user. Despite very strict regulation by government agencies, in the USA over 100,000 deaths per annum are attributed to adverse reactions to approved drugs.

In his investigation of improved methods of medical treatment by drugs, the inventor considered that at the beginning of evolutionary time, for survival, the earliest prokaryotes must have been able to detect internal and external elements of dissolved molecules and to act on this information. He termed this ability "sensezero".

Also it is now known that in multi-cellular animals complex cell signalling systems are used for motility, for survival and apoptosis, for example, and that these signals affect or control the maintenance of health and the progress of disease.

The inventor has also noted that many drugs which are formulated to pass into body circulation are not in fact metabolised in the body, but appear to achieve their therapeutic effect by their presence, and are then excreted unchanged.

The inventor therefore concluded that many drugs could have a therapeutic effect by being present in the environment of the body, but without entering circulation. The environment of the body he considered to be fluid. In the case of the skin and lungs the fluid is a gas i.e. air, and in the case of the gastrointestinal tract it is liquid.

The inventor does not wish to be bound by the hypothesis, but believes that the presence of a drug in the body environment but not in body circulation influences cell signalling and sensezero, and can therefore have a desired therapeutic effect without the drug being in circulation.

DESCRIPTION

Thus the present invention provides a medically efficacious compound coated or otherwise enclosed by an agent that forms a liquid impermeable but gas permeable barrier for use as a medicament. The inventor has termed the invention ActivSignal ™ class drugs.

The invention may be formulated in a variety of ways, including oral, buccal, nasal, sublingual, rectal, parenteral, topical, dermal or inhalational use, the formulations including nanoparticle and microparticle forms.

The invention provides for drugs to have a therapeutic effect without the undesirable side effects of drugs put into circulation, such as accumulation, toxicity or possible patient overdose. The invention gives the drug a consistent therapeutic effect as the "dose" is a constant and there is no metabolic change or metabolic by product. The invention improves the shelf life of drugs by excluding moisture. In the present invention some endogenous body substances may be used for a therapeutic effect, as such substances are formulated not to pass into circulation where they would have no effect.

In a most preferred embodiment of the present invention the active ingredient is formulated into oral administration tablets together with the excipients natural beeswax, cornstarch and talc. This method of manufacture is well known to those skilled in the art. Wax matrices are widely employed for drug delivery throughout the pharmaceutical industry because of the low production cost and ease of manufacture. In conventional drug delivery tablet manufacture the proportion of excipients by weight in the tablet is in the range of approximately 1% to 5%, and designed to facilitate immediate or delayed release of the active ingredient into solution. In this most preferred embodiment the excipients, mostly wax plus a small amount of

cornstarch and talc, are a proportion of the tablet mixture between 20% and 45% by weight. This novel method of manufacture is designed not to release any of the active ingredient into liquid solution, but the wax matrix is inherently gas permeable.

In a more preferred embodiment the active ingredient of the tablet is enclosed by a polymer and formulated to be liquid impermeable, but gas permeable. In preferred embodiment, the active ingredient may be enclosed by a ceramic and formulated to be liquid impermeable, but gas permeable. In a fourth embodiment the active ingredient may be enclosed within a metal tablet or capsule, such as perforated stainless steel, allowing passage of a gas but not liquid. Other embodiments include a pill, lozenge, bolus, capsule, caplet, granule or any suitable type, size or shape of manufacture, administered by any route, wherein the active ingredient is protected from contact with liquid but which is potentially contactable by a gas.

It is desirable to test the integrity of the liquid impermeability characteristic of a formulation, and that its physical integrity is preserved during use. A suitable in vitro test for a tablet, for example, is agitation in water adjusted to a pH of 3 with hydrochloric acid for three hours, followed by agitation in water adjusted to a pH of 7 with sodium bicarbonate for a further twenty four hours. The medication should not be changed to any significant degree by this test.

In vivo, after oral administration, a tablet may tested by being recovered from faeces, and should be found to be unchanged, or only changed to an insignificant degree, after passage through the body.

Drugs formulated according to the present invention may be formulated in nanoparticle or microparticle size. US Pat. No. 4622244 discloses the microencapsulation of an active by a suitable polymer to produce microcapsules of less than 300 microns in size i.e. suitable for injection in a suspension medium by means of small needles customarily employed in medical practice and thereby achieving controlled or sustained release of the active into body circulation. This method of manufacture is well known to those skilled in the art, and in the instance of the present invention the manufacture is achieved by encapsulation by a wax or polymer or other suitable barrier which is liquid impermeable but gas permeable. Particles may also be made up in a suspension for oral administration, as well as in gels, creams or pastes for dermal or any other administration.

Any embodiment may be made up for monotherapy or combined for multiple therapy as convenient. Any embodiment may include more than one active ingredient as convenient. Any embodiment may be combined with a preparation of any other active ingredient prepared for immediate or delayed or selective delivery into solution, as convenient.

Since the therapeutic effect of the invention depends on the presence of the drug in the environment of the body, arrangements need to be made to prevent desensitisation over time or the wearing off of the therapeutic effect. In the case of oral administration, desensitisation is avoided by the constant movement of the medicament through the gastrointestinal tract. In the case of administration by other routes it may be necessary for the present invented medicament to be provided and withdrawn at intervals, for example provided for three minutes in each thirty minutes, to avoid desensitisation. For example, a tablet of an ActivSignal ™ class drug according to the present invention may be placed on the skin and withdrawn at

intervals by use of a device including an electrical or other energy driven actuator held near to the skin of a subject. The same method is used where it is desired to surgically or otherwise implant an ActivSignal ™ class drug according to the present invention in the body of a subject. Alternatively, using fuzzy logic, very small quantities of the present invention formulated drug may be used at longer intervals. For example a dermal patch may be provided with two pellets of the drug formulated according to the present invention and of 2-3mm diameter and placed about 30mm apart with the patch being moved to a different location on the skin after each twenty four hours.

It will be appreciated that the amount of the drug used according to the present invention and the physiochemical properties of any agent employed to coat or otherwise enclose the drug will be influenced by the route of administration as well as a number of other factors including the health status of the subject being treated.

The invention is described in detail by the following examples which should not be construed as limitations on the scope or sphere of the invention in any manner.

EXAMPLE ONE

BACKGROUND

Cayenne pepper, a common food ingredient, is extracted from the chilli pepper (Capsicum annum) seed pod. The active ingredient of the pepper is the alkaloid capsaicin. Creams or lotions containing 0.025-0.075 % capsaicin are on sale and have a long history of use in dermatology for the treatment of itching and pain. When applied to the skin, capsaicin causes a burning sensation associated with depletion of neuropeptides from nociceptor nerve endings. Successful suppression of itch by topical administration has been reported for a number of pruritic dermatoses. [Hautarzt. 2000 Mar;51(3):164-72 PMID: 10789077 "Topical administration of capsaicin in dermatology for treatment of itching and pain"]

Atopic eczema (dermatitis) is a highly pruritic skin disease with patches of inflammation, weeping, blistering and bleeding if scratched. Many sufferers have disturbed sleep due to the constant itching. The open nature of the inflammation means that topical capsaicin with its burning sensation cannot be used to relieve eczema pruritus. Indeed topical capsaicin can induce dermatitis.

METHOD

Cayenne pepper was coated with a formulation of beeswax hardened with a small quantity of cornstarch and talc and compressed to form spherical pills of about 7mm diameter. According to the present invention these were made to be gas permeable but liquid impermeable ActivSignal ™ class drugs. Samples of the pills were agitated in vitro in acidic water for 4 hours, and alkaline water for 24 hours. The pills remained intact and no cayenne pepper was found in the water.

Six adult persons with atopic eczema (dermatitis) who had complained of pruritus and who were solely using topical preparations for relief were recruited. After informed consent was obtained each was asked to take one of the cayenne ActivSignal ™ class pills according to the present invention at 3pm and then not use their topical

medications until after 8 am the following morning. Each was asked to continue the treatment in the same manner for seven days. Each was asked each following day by telephone to rate their relief from overnight pruritus. Four subjects reported 100% relief on each of the seven nights as a result of the ActivSignal ™ class drug treatment. One subject reported 90% relief and one reported 50% relief as a result of the ActivSignal ™ class drug treatment. No adverse side effects were reported. Two subjects reported a feeling of warmth and slight sweating 2-3 hours after the first occasion of taking the pill.

It is concluded that a gas permeable but liquid impermeable preparation of cayenne pepper according to the present invention is effective for the treatment of eczema pruritus, with no adverse side effects reported.

EXAMPLE TWO

BACKGROUND

Metformin, a biguanide, has been available in the USA for the treatment of type 2 diabetes mellitus for nearly 8 years and in Europe for over 20 years. Over this period of time, it has become the most widely prescribed oral antihyperglycaemic agent. Its mechanism of action involves the suppression of endogenous glucose production, primarily by the liver. Whether the drug actually has an insulin sensitising effect in peripheral tissues, such as muscle and fat, remains somewhat controversial. Nonetheless, because insulin levels decline with metformin use, it has been termed an 'insulin sensitiser'. Metformin has also been shown to have several beneficial effects on cardiovascular risk factors and it is the only oral antihyperglycaemic agent thus far associated with decreased macrovascular outcomes in patients with diabetes. Cardiovascular disease, impaired glucose tolerance and the polycystic ovary syndrome are now recognised as complications of the insulin resistance syndrome, and there is growing interest in the use of metformin for these extraordinarily common metabolic disorders. While diet and exercise remain the cornerstone of therapy for insulin resistance, pharmacological intervention by use of metformin is now a well used alternative.

Metformin, however, is thought to sometimes accumulate in the body and thus increase the risk of lactic acidosis, a potentially fatal condition. Metformin therefore is considered to be contraindicated in many chronic hypoxemic conditions that may be associated with lactic acidosis, such as cardiovascular, renal, hepatic and pulmonary disease, and advancing age.

METHOD

Metformin 250mg was coated with a formulation of beeswax hardened with a small quantity of cornstarch and talc and compressed to form spherical pills of about 7mm diameter. According to the present invention these were made to be gas permeable but liquid impermeable ActivSignal ™ class drugs according to the present invention. Samples of the pills were agitated in vitro in acidic water for 4 hours, and alkaline water for 24 hours. The sample pills remained intact. On dissection no liquid was found to have entered the sample pills.

Five adult persons suffering from diabetes type 2 controlled by metformin alone were recruited. The group had been diagnosed with fasting plasma glucose (FPG) in the range 10 to 15 mmol/l before commencing the metformin treatment. Current dosages ranged from 500mg metformin twice daily to 850mg metformin three times daily. The five persons were controlling their FPG to below 8mmol/l and were taking weekly measurements with results in the range 5 to 8 mmol/l. Three of the five recalled having a metallic taste in the mouth occasionally and all five reported occasional abdominal discomfort as side-effects of taking metformin.

With informed consent, the five persons agreed to substitute the ActivSignal ™ metformin according to the present invention for the regular metformin at the rate of one ActivSignal ™ metformin pill for each regular metformin tablet they were currently taking, for a period of four weeks.

During the four week trial all of the five persons reported that they were controlling their FPG to below 8mmol/l whilst taking the ActivSignal ™ metformin. No side effects were reported.

It is concluded that ActivSignal ™ metformin according to the present invention has the equivalent therapeutic effect to regular metformin for persons suffering from moderate diabetes type 2, but that ActivSignal ™ metformin has reduced or no side effects. In addition, since ActivSignal ™ metformin is not released into the body there can be no accumulation, so that ActivSignal ™ metformin is suitable to be tested with persons where currently contraindicated for the therapy of chronic conditions that may be associated with lactic acidosis.

EXAMPLE THREE

BACKGROUND

Aspirin is the acetyl derivative of salicylic acid that is used to lower fever, relieve pain, reduce inflammation, and thin the blood. Common conditions treated with aspirin include headache, muscle and joint pain, and the inflammation caused by rheumatic fever and arthritis. Aspirin is believed to act against fever, pain, and inflammation by interfering with the synthesis of specific prostaglandins in the body. Because of its ability to inhibit the formation of blood clots, aspirin is also used in low doses to prevent heart attack and stroke and to control unstable angina. The drug's usefulness in preventing certain cancers, the dangerous high blood pressure that sometimes occurs during pregnancy (toxemia), and migraine headaches has also been reported.

Normal dosage of aspirin may cause nausea, vomiting, diarrhoea, or gastrointestinal bleeding. Large doses cause acid-base imbalance and respiratory disturbances and can be fatal, especially in children. Aspirin also has been linked to the development of Reyes' syndrome (a combination of acute encephalopathy and fatty infiltration of internal organs) in children who have taken it for viral infections. Acetaminophen (paracetamol) which does not cause gastric irritation, lowers fever and relieves pain but does not reduce inflammation, is often substituted for aspirin. Ibuprofen is a suitable substitute for aspirin and may be taken for up to ten days without prior consultation with a physician. Ibuprofen may have similar side effects to aspirin although these are less common.

Salicylic acid or 2-hydroxybenzoic acid, C6H4(OH)CO2H, is colourless, crystalline organic carboxylic acid used as an oral administered analgesic up to the end of the nineteenth century, until the invention of the less irritating acetyl derivative, aspirin. Other derivatives of salicylic acid are used as an active ingredient of many topical preparations including sun creams, toothpaste, and antiseptics and they are also used as a food additive. Aspirin is the most widely used medication in the world with over 80 billion doses sold annually in the USA alone, and aspirin is an active ingredient in over fifty over-the-counter medications.

METHOD

Pharmaceutical grade aspirin was hydrolysed to salicylic acid and then coated with beeswax hardened with cornstarch and talc and compressed to form pills of about 6mm diameter. According to the present invention these were made to be gas permeable but liquid impermeable ActivSignal ™ class drugs. Samples of the pills were agitated in vitro in acidic water for 4 hours, and alkaline water for 24 hours. The sample pills remained intact. On dissection no liquid was found to have entered the sample pills.

Twelve adult persons were recruited who were taking aspirin or acetaminophen (paracetamol) or ibuprofen ad lib for the relief of mild to moderate arthritic pain, at up to the maximum recommended dose per day, namely 12 x aspirin 300mg, or 8 x acetaminophen 500mg or 6 x 200mg ibuprofen. Some of the group were taking combined aspirin and acetaminophen up to the combined recommended daily dosage.

With informed consent members of the group agreed to substitute their regular analgesic with ActivSignal ™ salicylic acid pills for three weeks. They were advised to start, when required, with one ActivSignal ™ salicylic acid pill per day or two (one morning, one evening) if required. They were advised, if necessary, they could take (one at a time) up to six pills per day with a minimum two hour interval. At the end of the trial six persons reported that the ActivSignal ™ salicylic acid pills were more effective at relieving pain than their regular analgesic. A further five persons reported that the ActivSignal ™ salicylic acid pills gave about the same level of pain relief as their regular analgesic. These eleven persons had taken either one, two or three ActivSignal ™ salicylic acid pills on most days. None had found the need to take more than three of the pills on any day. All reported that the pain relief seemed to be longer lasting with the ActivSignal ™ salicylic acid pills than with their regular analgesic. No side effects were reported. One person found the ActivSignal ™ salicylic acid pills less effective than the ibuprofen she was normally taking, and dropped out of the trial.

It is concluded that ActivSignal ™ salicylic acid according to the present invention is an effective and long lasting analgesic with no reported side effects.

EXAMPLE FOUR

BACKGROUND

Essential hypertension is one of the major health problems of the developed world, affecting over 20% of the adult population. Essential hypertension is defined as persistent high pressure of unknown cause. Untreated essential hypertension can lead

to heart attack (myocardial infarction), congestive heart failure, other heart damage, arteriosclerosis, kidney damage, stroke and loss of vision.

The inventor has found that the main cause of essential hypertension is the prevalence of asymptomatic miliaria profunda in the population of advanced societies, this disease causing inflammation which raises pressure in skin blood capillaries. The miliaria is a result of over conservation of sodium by sweat gland ducts. It follows that by using ActiveSignal ™ class drugs containing sodium the over conservation can be reversed, and the miliaria and thus the essential hypertension is prevented.

The classification of blood pressure in adults by the World Health Organisation and the International Society of Hypertension (revised 1999) is as listed in Table 1.

TABLE 1

Classification	Systolic		Diastolic
Optimal	<120	and	<80
Normal	<130	and	<85
High-normal	130-139	or	85-89
Mild hypertension	140-159	or	90-99
Moderate hypertension	160-179	or	100-109
Severe hypertension	>180	or	>110

All values are mmHg. Measurements are taken with subjects in the sitting position.

Sodium chloride or common salt occurs naturally in many parts of the world. Chemically, sodium chloride is 60.663% elemental chlorine and 39.337% sodium. Sodium chloride crystals are cubic in form and are readily available as a pure chemical.

Sodium chloride is an endogenous substance of the mammalian body, and essential to the maintenance of life, but ordinary intake of the chemical has never been found to have a therapeutic effect. Indeed restriction of intake of sodium chloride is recommended for persons with essential hypertension.

METHOD

Pure sodium chloride was coated with beeswax hardened with cornstarch and talc and compressed to form pills of about 6mm diameter ActivSignal ™ class drug and granules of about 2mm diameter ActivSignal ™ class drug, both according to the present invention being liquid impermeable but gas permeable. Two each of the granules were fixed to an adhesive hypoallergenic patch at a distance of about 30mm.

Following informed consent nine persons with mild, moderate or severe hypertension were asked to participate in a trial. Before commencement of the trial, the blood pressure of each person was measured after the subject had been at rest seated for fifteen minutes. After a further ten minutes the blood pressure was measured again and the average of the two systolic readings and the average of the two diastolic readings was noted. Measurements were taken using the Omron 705IT Blood

Pressure monitor, a clinically validated machine. Small, medium and large cuffs were available and selected according to the manufacturers instructions.

The subjects were then asked to fix the patch with the two ActivSignal ™ class drug granules anywhere on the front of their abdomen. Further, a new patch was fixed in a different position after each twenty four hours for a further three days and each time the used patch discarded. The subjects were also given one of the 6mm diameter pill ActivSignal™ class drugs taken orally with about 200ml water on the first and third days of the trial.

Blood pressures were taken in the same manner after 1, 2, 4 and 6 days of the trial.

At the start of the trial four of the persons had mild hypertension, three had moderate hypertension and two had severe hypertension. After four days, measurements of blood pressure as listed in Table 2 show that following treatment the systolic blood pressure had been reduced by 27% and the diastolic pressure by 18%.

After four days six subjects were now within the "optimum" classification of blood pressure, and two were now within the "normal" classification. One of the subjects originally having severe hypertension was now classified as having mild hypertension. After six days, as shown in Table2, the benefits of the treatment persisted after the treatment had been discontinued.

These data illustrate that the use of sodium chloride as an ActivSignal ™ class drug according to the present invention may easily and rapidly reduce blood pressure to within normal limits so that the subjects can no longer be considered hypertensive. The treatment has the effect of restoring skin blood capillaries to their natural free flowing function.

The invention has the effect of resetting blood pressure to what is considered normal. Essential hypertension is known to be only a slowly progressive disease and it can therefore be anticipated that following treatment the subjects are unlikely to become hypertensive again for many months or some years, when the treatment can be repeated.

Compared with treatments with current pharmaceutical products which need to be taken daily for a lifetime, which have unpleasant side effects, and which do not treat the underlying disease, the present invention is a much swifter, more effective and less costly treatment of essential hypertension with no known side effects.

TABLE 2

Subj No. M/F Age		Before Trial	After 1 day	After 2 days	After 4 days	Percentage reduction	After 6 days
(01) F55	Syst	158	139	122	108	31%	106
	Diast	88	74	67	62	30%	58
(02) M62	Syst	162	135	121	103	35%	102
	Diast	89	78	70	58	33%	47
(03) M55	Syst	157	122	122	118	24%	120
	Diast	77	78	78	68	9%	72
(04) F49	Syst	196	160	124	122	37%	128
	Diast	96	93	81	78	18%	78
(05) F50	Syst	157	122	122	123	21%	122
	Diast	72	72	72	70	2%	70
(06) M65	Syst	175	167	157	154	12%	155
	Diast	90	90	90	85	5%	86
(07) M52	Syst	188	149	131	128	31%	125
	Diast	108	96	88	78	27%	79
(08) F54	Syst	146	135	129	114	15%	119
	Diast	88	83	83	77	12%	80
(09) M52	Syst	162	140	133	116	22%	116
	Diast	98	90	89	80	18%	78

I CLAIM

1. A preparation comprising a medically efficacious substance coated or otherwise enclosed by an agent that forms a liquid impermeable but gas permeable layer for use as a medicament.

2. A medically efficacious substance for the remedying or prophylaxis of disease formulated such that the substance cannot cross epithelial barriers in mammals.

3. A medically efficacious substance for the remedying or prophylaxis of disease formulated such that the substance cannot cross membrane barriers in mammals.

4. A medically efficacious substance for the remedying or prophylaxis of disease formulated such that the substance cannot cross into cells of mammals.

3. A preparation according to claims 1 or 2 or 3 or 4 in the form of a pill.

4. A preparation according to claims 1 or 2 or 3 or 4 in the form of a tablet.

5. A preparation according to claims 1 or 2 or 3 or 4 in the form of a lozenge.

6. A preparation according to claims 1 or 2 or 3 or 4 in the form of a bolus.

7. A preparation according to claims 1 or 2 or 3 or 4 in the form of a capsule.

8. A preparation according to claims 1 or 2 or 3 or 4 in the form of a caplet.

9. A preparation according to claims 1 or 2 or 3 or 4 in the form of a granule.

10. A preparation according to claims 1 or 2 or 3 or 4 in the form of a gel.

11. A preparation according to claims 1 or 2 or 3 or 4 in the form of a nanoparticle.

12. A preparation according to claims 1 or 2 or 3 or 4 in the form of a microparticle.

13. A preparation according to claims 1 or 2 or 3 or 4 in any form similar to any of the forms included in claims 3 to 12.

14. A preparation according to claims 9 or 11 or 12 provided in a suspension.

15. A preparation according to claims 9 or 11 or 12 provided in a cream.

16. A preparation according to claims 9 or 11 or 12 provided in a paste.

17. A preparation according to claim 1 or 2 or 3 or 4 prepared for use with a patch for holding the said preparation near to or against the skin.

18. A preparation according to claim 1 or 2 or 3 or 4 prepared for implantation of the said preparation in the body.

19. A preparation according to claim 1 wherein the agent is a ceramic.

20. A preparation according to claim 1 wherein the agent is a polymer.

21. A preparation according to claim 1 wherein the agent is a natural wax.

22. A preparation according to claim 1 wherein the agent is beeswax hardened with cornstarch and talc.

23. A preparation according to claim 1 or 2 or 3 or 4 wherein the substance is sodium chloride.

24. A preparation according to claim 1 or 2 or 3 or 4 wherein the substance is capsaicin.

25. A preparation according to claim 1 or 2 or 3 or 4 wherein the substance is metformin.

26. A preparation according to claim 1 or 2 or 3 or 4 wherein the substance is salicylic acid.

27. A preparation according to claim 1 or 2 or 3 or 4 wherein the substance is a derivative of salicylic acid.

28. A preparation according to claim 1 or 2 or 3 or 4 wherein the substance is the same as a substance endogenous to the body of the subject.

29. A preparation according to claim 1 or 2 or 3 or 4 wherein the substance is a food substance.

30. A preparation according to claim 1 or 2 or 3 or 4 wherein the substance is a drug.

27. A preparation according to claim 1 or 2 or 3 or 4 prepared for use with a device for holding the said preparation near to or against the skin.

28. A preparation according to claim 23 where the substance is substantially pure sodium chloride.

29. A preparation according to claim 24 where the substance is extracted from Capsicum Annum.

30. A preparation according to claim 1 wherein the substance is extracted from a plant.

31. A method of making a pharmaceutical composition substantially as described herein with reference to the accompanying Examples.

32. A medically efficacious substance administered by any route wherein the substance is protected from contact with liquid but where the substance is potentially contactable by a gas.

33. A preparation according to claim 32 formulated to extend the shelf life of the preparation.

34. Any preparation according to the preceeding claims combined with any one or more preparations according to the preceeding claims.

35. Any preparation according to the preceeding claims combined with a preparation of any ingredient or ingredients designed for delivery into solution.

36. Any preparation according to the preceeding claims combined with a preparation of any ingredient or ingredients designed for delivery into solution for a therapeutic purpose.